REMARKS

In a prior amendment applicants elected without traverse, Group I, species A, which read on claims 1-4, 7-11 and 34, in our reply filed on October 30, 2007.

Claims 5, 6, 24-27, 31-33 and 35 are withdrawn from further consideration as being drawn to a nonelected invention.

Claims 1-4, 7-11, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burd et al. (US 5,939,331) in view of Killeen et al. (US 5,166,051).

Burd et al. is relied upon for teaching a test device (biosensor). The Office Action states that the device is made of plural layers of porous material, said device having a labeling zone 26 (reagent holding part) which holds a labeled reagent for analyzing an analyte in a whole blood sample (liquid specimen having cell components contained therein). The device analyzes target components in the sample by utilizing chromatography. The device further includes a matrix 23 carrying a cell-binding reagent having the ability of immobilizing cell components of a blood sample on at least a part of an area of said matrix, with the area ranging from a sample (specimen) addition part to which the sample is added to a labeling zone 26. The device further includes a nitrocellulose section 27 with capture zone 29 (reaction layer) chromatographically downstream of matrix 23 on which a reaction between the analyte in the blood sample and the labeled reagent eluted from the labeling zone is carried out which allows for analysis of the analyte in the blood sample (see Figure 1; column 2, lines 8-62; column 5, lines 6-38; column 8, lines 14-67; column 9, lines 1-67; and column 10, lines 1-14).

The Office Action concedes that Burd et al fail to teach that the matrix includes a cell shrinkage reagent having the ability of making the cell components of said blood sample (liquid specimen) shrink, wherein the shrunk cell components are made smaller by the cell shrinkage reagent.

Killeen et al. is relied upon for teaching a diagnostic test strip for chemically determining whole blood analytes which includes a support, a porous detection zone

membrane, and an overlay membrane in overlying and continuous contact with the detection zone membrane. A sample of whole blood is applied to the overlay membrane which contains an effective amount of a crenating agent. The crenating agent functions to deplete the volume of fluid within the red blood cells, which shrinks and rigidifies the cells, making them less flexible. The rigidified cells are less able to penetrate into the pores of the detection zone membrane, which allows for the passage of analyte that has been released from the solution of the whole red blood cells into the detection zone membrane (see Abstract; and column 5, lines 5-61).

The Office Action states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to include with the device of Burd et al. a cell shrinking reagent within the sample addition matrix as taught by Killeen et al. The reason for combination of art is that Killeen et al. teach the benefit of including a crenating (cell shrinking) reagent within a sample addition membrane, i.e. overlay membrane, of a test strip used in determining whole blood analytes because the crenating agent functions to deplete the volume of fluid within the red blood cells of a blood sample, which shrinks and rigidifies the cells, making them less flexible and less able to penetrate into the pores of the detection zone membrane. This allows for the passage of analyte that has been released from the solution of the whole red blood cells into the detection zone membrane.

With respect to claim 2, the Office Action states that Burd et al. teach that the sample is whole blood (see Abstract).

With respect to claim 3, Killeen et al. is relied upon for teaching that the liquid specimen, i.e. sample, can include bacteria (see column 6, lines 17-18).

With respect to claim 4, Killeen et al. is relied upon for teaching that the cell crenating (shrinkage) reagent is an inorganic salt (see column 5, lines 48-61).

With respect to claims 7 and 9, Killeen et al. is relied upon for teaching that the cell crenating reagent is dried naturally or air-dried with heat (see column 10, lines 34-39).

With respect to claim 8, the Office Action states that Burd et al. teaches that the cell reagent applied to the sample matrix can be dried or lyophilized (see column 5, lines 6-12; and Example 1).

With respect to claims 10-11, Burd et al. is relied upon for teaching that the test device is a dry analytical element in the form of a one-step immunochromatographic test strip (see Abstract; Figure 1; column 9, lines 57-67; and column 10, lines 1-14).

With respect to claim 34, Killeen et al. is relied upon for teaching that the crenating reagent, preferably in the form of sodium chloride, should have a concentration from about 0.85 to about 35% (see column 5, lines 64-68; and column 6, lines 1-8).

No claims have been allowed.

Reconsideration of the present invention is requested in view of the following remarks and attached Exhibit which explains the penetration of the whole blood specimen according to the present invention.

The biosensor of the present invention is made of a single layer or plural layers of a porous material, with the biosensor having a reagent holding part and utilizing chromatography, wherein a cell shrinkage reagent is carried on at least part of the reagent holding part, or at least part of a chromatographically developed part which is upstream of the reagent holding part.

In contradistinction to the present invention, Killeen et al. extracts fluid and makes red blood cells shrink by the crenating agent such as inorganic salt which is included in the overlay membrane.

Burd et al. teaches a method and device which includes a sample receiving zone which removes red blood cells from the sample by using a red blood cell binding reagent, a labeling zone which contains a labeling reagent, a capture zone which contains an immobilized capture reagent, and an absorbent zone. The Burd et al.

device is constructed so as to make the component of the sample flow, which does not include red blood cells.

The rejection purposes combining Killeen et al. in which fluid is extracted from the cell, only fluid penetrates into the pores of the detection zone membrane, and rigid cells cannot penetrate the pores, and Burd et al., in which the red blood cells by a red blood cell binding reagent are removed, and which employs the blood sample which does not include the red blood cells. It is submitted that the proposed combined device cannot function without being clogged with cell pieces, carry out an immune reaction without the recessing of previously carrying out any pre-processing, as in the present invention.

The following information is provided as background information in order to explain the features of the present invention in addressing and overcoming the problems and needs of the art of biosensors.

Initially, a laboratory specimen which is mainly assumed in the present invention is the whole blood, and the whole blood is the laboratory specimen which is used widely at the present time in clinical settings for the purpose of diagnosing the conditions of a living body. Generally, in carrying out a clinical test in a hospital, the whole blood specimen, which is withdrawn through a syringe, is placed in a test tube which is encapsulated with anticoagulate such as heparin. The test tube is directly placed into a centrifuge as a centrifuging tube, with the centrifuging technique resulting in the component of blood cells, which is a formed element precipitate, being segregated in a short time, as compared to the case where it is left at rest. After the segregation, serum and blood plasma, which are the clear upper portion, are extracted and analyzed. These are processes are in current usage even as of the time of filing the present application. There may be a system in which is the centrifuge function is integrated into the test system. However, in any case, the centrifuge processing is needed, and the component of serum or blood plasma is extracted and analyzed.

In contrast, in Point Of Care Testing (POCT), which also relates to the present invention, to carry out centrifuging as in this way is controversial from the viewpoint of

such as the volume of the equipment (size), the experimental skill, and the cost. Therefore, the prior art which is discussed in the present application is thought to be, as an extension of the idea of "segregating blood cells", constructed to have the function to filtrate formed element such as red blood cells. That is, it is understood that in the prior art, it is a general and obvious idea of a person skilled in the art to segregate the whole blood into formed element and fluid element, as an extension of the large size analysis apparatus in a clinical test. It is also shown in Killeen reference that formed element is removed, in summary and column 2, line 23-26 and line 28-35, though the construction is different in the present invention.

However, in Point Of Care Testing (POCT), as compared with the large-scale clinical test system, it is especially required to employ minute blood specimen, and that the device is small-sized, that the operation is easy, and it is possible to obtain rapid measurement results. Moreover, the precision in measurement is needed in view of the range of clinical significance of the measurement. Such market needs and the above-mentioned respective arts are compared as follows.

In the whole blood specimen, the prior art which is constituted to filtrate formed element and not make the same reach a reaction part, cannot use all of the collected specimen volume for the reaction, because there arise losses of the specimen volume due to the filtration. Therefore, there is a need to collect a great amount of specimen compared to the required amount for the reaction with considering at least the loss of the volume by the filtration.

In contradistinction to the above, the present invention is constituted so that all of the specimen develops in a reaction layer, and almost all the specimen volume collected can be used for the reaction. See the attached Exhibit which illustrates the penetration of the whole blood specimen over a 30 second to 1 minute time frame. When comparing both of these, the constitution of the present invention can carry out a measurement of a minute specimen, that is needed in Point Of Care Testing (POCT).

Further, when the formed element is filtrated from the whole blood, the filtration must be carried out upstream relative to a reaction part in the measurement, but the

whole blood specimen is not uniform in all individuals, and the differences in individuals can be very large. For example, the volume proportion of blood cell component of the whole blood, which is usually indicated as Haematocrit value, is 39.8%-51.4% for men, and 33.4%-44.9% for women and quite different for individual (reference 1). Moreover, the average level for healthy young children is further varied for the individual, as 44%-64% for newborns (umbilical blood), 32%-44% for baby after 3 months of age, 36%-44% for one-year-old baby, and 37%-44% for ten to twelve-year-old children (reference 2) . It should also be pointed out that there is a further larger range than these values for the values of disorders. That is, when comparing values for healthy individuals in the references, the volume of formed element included in the whole blood specimen of the same volume differs by about 30%. The volume of red blood cells which are filtrated from the specimen having small number of red blood cells and the volume and the number of red blood cells which are filtrated from the specimen having large number of red blood cells are quite different, and there maybe cases where the clogging occurs in the filtration part as extreme cases. Even when the clogging would not occur, the physical deposition of formed element which accounts for 1/3-1/2 in the whole blood onto the filtration part may prevent the blood serum or plasma component from penetrating. After the start of the measurement, as the deposition amount increases with the passage of time, the influence may become larger, and there may arise quite a large change in the flow of blood serum to downstream. Since the Killeen reference is quite different in its constitution from the present invention, it is not clear whether this change of the flow of blood plasma to downstream affects the reaction or the measurement, according to the constitution of Burd reference. The uneven flow of specimen solution and the change of flow volume of the solution involved in the reaction would have an extraordinary effect on the reaction layer, thereby resulting in significantly inaccurate measurement result. It is assumed that the individual differences would even increase this problem, and this shows that the clinical test is one for testing the condition of human body, which may include, in some cases, quite serious problems involving human lives due to erroneous measurements.

Moreover, in the filtration technique, the filtration processing is needed, and therefore the increase of processings in the measurement happens compared with the

present invention which has no need to perform filtration. While in that technique a series of flow comprising addition of specimen solution, a filtration, a reaction, and a detection are assumed, since there is an increase in the processing and the formed element inhibits the flow of blood plasma physically, the measurement time increases, thereby resulting in no quick measurement as compared with the present invention. Moreover, the increase in the constituent material for performing filtration is generated, and thereby there arises increase in the material cost and the production cost.

In other words, as proposed in the Office Action supposing that Killeen is combined with Burd and the constitution to filtrate could have been used at upstream in the constitution of Burd, a lot of specimen is needed due to the filtration, and the precision of measurement accuracy is deteriorated, the measurement time becomes longer, the constitution becomes complex, and there arises an increase in cost. Therefore it is quite clear that it is not possible to obtain the effect of the present invention by combining the two references.

While the person skilled in the art may have been in a position to know that measurements cannot be performed unless the formed element of the whole blood specimen is filtrated, over a long period of time, the present invention address and solves these technological issues. In view of these facts it is submitted that the features of the claimed invention are not described or suggested by the combination of Killeen and Burd. Even if Killeen reference and Burd reference, which do not describe and suggest the construction of the present invention, are combined, the combination does not result in the present invention. In the first place, Killeen teaches that the overlay membrane includes an effective amount of creating agent which eliminate the red blood cells from the detection zone membrane, that the red blood cells become rigid and are less flexible by crenating, and that they do not penetrate due to the pores of the detection zone membrane (column 2, lines 23-26 and lines 28-35). Therefore, Killeen fails as a reference in that the effect of the present invention cannot be obtained by using Killeen as a reference which has a characteristic that cell components do not move to the detection zone, that is, that “the filtration” is carried out, and the Burd reference, which has a construction similar to that of the present invention, cannot be

effectively modified by Killeen to remedy the deficiencies of Burd. Further, to clarify the characteristics of the present invention which does not carry out filtration, with the claims amended, in response to a previous Office Action.

Reconsideration of the present invention and withdrawal of all rejections of record (claims 1-4, 7-11 and 34) is hereby requested in view of the arguments presented herein and the attached exhibit.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 50-0289, under Order No. 967_026RCE from which the undersigned is authorized to draw.

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Respectfully submitted,

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Reference 1: The clinical test data book, 2007—2008, published in March 1, 2007. Igaku-Shoin Ltd., p.339.

Reference 2 : The clinical test method outline, published in September 20, 1998. KANEHARA & Co., LTD., p.271.